REMARKS

In the Office Action of December 20, 2007, the Examiner maintained the rejections of claims 46-48 under 35 U.S.C. § 103(a) for being obvious over Roberts taken in view of Lund.

The rejection of claims 46-48 over Roberts in view of Lund is respectively traversed. Roberts is directed to clostridial vaccines "made without stabilizing carriers or depot adjuvants, but rather with a readily dispersible, water-soluble adjuvant, saponin." (Page 1, paragraph 1). The only dosage ranges suggested by Roberts are specifically for the water-soluble adjuvants. Roberts provides no descriptions or examples of clostridial vaccines including antigens other than clostridials. It only mentions in passing that non-clostridials may be added such as *M.bovis*, *H.somnus* and *P.hemolyticum*. (Page 5, line 13).

Lund is relied on for teaching adjuvant polymers that are retained at the site for prolonged slow release wherein the active agent is absorbed into the polymer; that is, depot adjuvants.

Although mentioning all varieties of adjuvants, Roberts clearly teaches that multicomponent clostridial vaccines should be made up using readily dispersible, water-soluable adjuvants rather than depot adjuvants, including carbopol, because those adjuvants "usually provoke severe persistent local reactions, which are reported to be "responsible for carcass blemish which requires expensive trimming, a consideration when the vaccine has been injected into muscle tissue destined to be a valuable cut of meat." Roberts teaches against using polymeric adjuvants and in favor of using readily dispersible, soluble adjuvants. Furthermore, the dosage ranges disclosed apply specifically to "vaccines of the present invention," the vaccines with soluble adjuvants.

The Examiner improperly, therefore, combines the teaching found in Roberts with Lund, which as the Examiner states, "teaches an adjuvant polymer, such as CARBOPOL™, [which] is retained at the site for prolonged slow release that acts by absorbing the active agent onto the polymer". (Columns 1-2, lines 67-5).

One of ordinary skill in the art reading Roberts would never find reason to combine it with

Lund as the teachings are directed to different types of adjuvants, the readily dispersible adjuvants of Roberts, versus the depot adjuvants of Lund. The Examiner, respectfully, misconstrues the teachings of these references, which clearly conflict.

That is, Roberts teaches that low tissue reactivity is accomplished using dispersible, soluble adjuvants. "The present invention is based on the surprising discovery that the water soluble adjuvant, saponin, can be used in place of a depot adjuvant in multicomponent clostridial vaccines for cattle." (Page 2, lines 22-24).

On page 1, the first full paragraph, Roberts states:

> "The present invention relates generally to vaccine compositions and methods of using the same. More specifically, the invention pertains to multicomponent clostridial vaccines **made without** (emphasis added) stabilizing carriers or **depot adjuvants** (emphasis added), but rather with a readily dispersible, water-soluble adjuvant, saponin."

Roberts teaches against using encapsulating adjuvants, such as those used in Applicants' invention and those to which Lund is directed. On page 2, the paragraph beginning on line one, Roberts recites:

> "Other potent **depot adjuvants** (emphasis added), such as water-in-oil emulsions and carbopol, have also been used in clostridial vaccines. The above-described adjuvants, although increasing antigenicity, **usually provoke severe persistent local reactions** (emphasis added), such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly. These local reactions are, in turn, responsible for carcass blemish which requires expensive trimming, a consideration when the vaccine has been injected into muscle tissue destined to be a valuable cut of meat."

On page 4, in the paragraph beginning on line 24, Roberts states:

> "**Central to the present invention is the surprising discovery** (emphasis added) that stable, potent, multicomponent clostridial vaccines can be made **without the use of depot adjuvants** (emphasis added). In particular, the present invention provides for vaccines including rapidly dispersed, soluble adjuvants, that is, **adjuvants that are not retained at the injection site for a significant period of time, thereby exhibiting low tissue reactivity** (emphasis added). The vaccines can be administered intramuscularly and subcutaneously without the harmful side effects and chronic inflammatory responses that produce granulomas and abscesses, seen with other clostridial vaccine compositions when administered via these routes."

Roberts clearly teaches against using an encapsulating polymer adjuvant that releases antigens slowly at the site of injection. Any skilled practitioner reading Roberts must conclude that using such polymer adjuvants would result in high incidents of "severe persistent local reactions, such as granulomas, abscesses and scarring," that would in turn be "responsible for carcass blemish which requires expensive trimming." Applicants teach using such encapsulating polymer adjuvants and yet they achieve the minimization of injection site lesion formation (a reduction of at least 41%) by administering 2 ml doses rather than conventional 5 ml doses. Unexpectedly in view of the prior art, Applicants also achieved protective immunity using a depot adjuvant in a 2 ml dose.

The ordinary practitioner would never, based on the teaching of Roberts, exchange the adjuvant of Roberts for an equivalent encapsulating polymer, as Roberts clearly teaches that such polymer adjuvants result in deleterious injection site lesion formation. Roberts does not suggest in any way that these problems could be overcome with low dose encapsulating polymer formulations.

In view of the clear teaching by Roberts to not use encapsulating polymers, the ordinary practitioner would never combine the teachings of Roberts and substitute an encapsulating polymer in view of Lund. Following the teaching of Lund, which is the use of a prolonged

release polymer adjuvant, it would be expected, based on Roberts, to "provoke severe persistent local reactions, such as granulomas, abscesses and scarring,..." that "are, in turn, responsible for carcass blemish...." (page two, first paragraph). The ordinary practitioner reading Roberts would never adopt the use of the adjuvant polymers, at any dosage, taught by Lund.

The Supreme Court stated in KSR (*KSR International Co. v. Telefax Inc.*, 127 S. Ct.1727 (2007)) that Graham factors still control the obviousness inquiry. Those factors are: 1) "the scope and content of the prior art;" 2) "differences between the prior art and the claims;" 3) "the level of ordinary skill in the pertinent art;" and 4) "objective evidence of non-obviousness". *KSR, 127, S. Ct. at 1734* (quoting *Graham v. John Deere Co. of Kansas City*, 86 S. Ct. 684 (1966)). Addressing these factors, the scope and content of the prior art include separate and opposing teachings by Roberts and Lund, one directing the ordinary practitioner to soluble adjuvants and the other directing the practitioner to depot adjuvants. The differences between the prior art and the claims include the prior art teaching that soluble adjuvants are required to reduce injection site lesion formation contrasted with Applicants' use of depot adjuvants while still reducing injection site lesion formation, and thus the reduction of spoilage. The level of ordinary skill in the art is relatively high, more than sufficient for the ordinary practitioner to conclude, reading Roberts, that depot adjuvants would result in injection site lesions. Again, in view of Roberts, the objective evidence of non-obviousness is Applicants' use of depot adjuvants, encapsulating polymer adjuvants, which result in the slow release of antigen at the site of injection, but, at the same time, reducing injection site lesion formation. The primary reference teaches against using encapsulating polymer adjuvants and the secondary reference, in addition to being inconsistent with the primary reference, does not address the reduction of injection site lesions.

In view of the above, Applicants respectfully submit that the Examiner has made an improper combination of prior art references as they reveal to the skilled practitioner two opposing teachings for selecting adjuvants and, further, relying on a primary reference that teaches against Applicants' use of encapsulating polymer adjuvants and the use of the adjuvants

of the secondary reference.

Applicants do not concede that Roberts teaches vaccine in 2ml dosages, however, even if it did, the ordinary practitioner could only conclude that the 2ml dosages would apply to vaccines based on soluble adjuvants and not vaccines comprising depot adjuvants, such as Applicants' encapsulating polymer adjuvants. Even if Roberts is interpreted to teach such low dose vaccines, Roberts is directed to "the surprising discovery that the water-soluable adjuvant, saponin, can be used in place of a depot adjuvant in multicomponent clostridial vaccines for cattle." (page 2, lines 21-24). On page 8 of Roberts, the formulation of the "dispersible, non-depot adjuvant" composition is described and, although dosages are merely mentioned in passing, giving broad ranges, the dosages ranges mentioned specifically refer to "vaccine compositions of the present invention." "For example, to immunize cattle with the clostridial vaccine compositions described above, [dispersible, non-depot adjuvant compositions] generally between 0.5 ml to 10 ml will be administered, more preferably 1 to 5 ml." (page 8, lines 30-32). No mention is made for dosage ranges used with other, non-dispensible adjuvants. Furthermore, beyond the broad ranges mentioned, as noted above, all specific examples of such saponin, soluble adjuvant vaccine compositions were administered to cattle using 5 ml dosages (Example 3, pages 13-18).

Claims 46-48 stand rejected under 35 U.S.C. § 112, first paragraph, for not providing sufficient written description. The Examiner objected that Applicants did not point to the support in the specification showing that injection site lesion formation was reduced at least 40% compared with an injection of 5 ml of the same vaccine. The Examiner did not accept Applicants' direction to page 54, Tables 12 and 13, for support, alleging that after weaning the reduction was only 33.2%.

The rejection under 35 U.S.C. § 112, first paragraph is respectfully traversed. In Table 12 on page 54, the reduction in the number of lesions from the 5 ml dose when using the 2 ml dose is from 79.5% of the cattle to 46.3% of the cattle, a reduction of 41% in the number of cattle having lesions. The specific types of lesions are reported in Table 13. Applicants believe that these results support a limitation as presently set forth in the claims that injection site lesion

formation is reduced at least 40% compared with an injection of 5 ml of the vaccine. However, in order to advance the prosecution of this application, the limitation in the claims is now changed to a reduction of at least 41%, which is supported by these Tables. The "at least" term finds support in Table 14 on page 55, wherein the incident of lesions is reduced from 69.4% to 30.3%, an overall reduction of 56.3%.

The above mentioned dramatic reductions in lesion formation further support the non-obviousness of the present invention. In view of the above it is believed that claims 46, 47 and 48, as now amended, are in condition for allowance. Favorable action is solicited. Should the Examiner consider that a conference would be helpful in advancing the prosecution of this application, she is invited to telephone the Applicants' attorney at the number below.

Pursuant to 37 C.F.R. § 1.116, Applicants submit that the amendments presented herein are made to comply with a requirement of form expressly set forth in a previous Office action, and present rejected claims in better form for consideration on appeal.

Applicants do not believe that any other fee is due in connection with this filing. If, however, Applicants do owe any such fee(s), the Commissioner is hereby authorized to charge the fee(s) to Deposit Account No. 02-2334. In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. 02-2334.

Respectfully submitted,

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